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Population-Based Incidence and Survival Figures in Essential Thrombocythemia and Agnogenic Myeloid Metaplasia: An Olmsted County Study, 1976–1995

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To provide basic information about occurrence and outcome of essential thrombocythemia (ET) and agnogenic myeloid metaplasia (AMM), we used the Rochester Epidemiology Project medical record linkage system for residents of Olmsted County, Minnesota. We identified all residents who were diagnosed with ET or AMM from 1976 to 1995. Community inpatient and outpatient medical records were reviewed to verify the diagnosis of ET or AMM, and patients were followed passively through their medical records to determine the outcome after diagnosis. We identified 39 cases of ET and 21 of AMM, with age- and sex-adjusted incidence rates of 2.53 and 1.46 cases/100,000 population annually, respectively. The respective median ages at diagnosis were 72 and 67 years. The female-to-male ratios were 1.8 and 1.6 for ET and AMM, respectively, and when adjusted for age, there was no difference in risk. The median follow-up period was 62.9 months for ET and 33.2 months for AMM. Five- and 10-year survivals were 74.4% and 61.3%, respectively, for ET and were significantly lower than expected for age-matched controls ($P = 0.012$). Prognosis was worse for AMM, with a median progression time of 7 months and a 3-year survival of 52.4%. This was significantly worse than for age-matched controls ($P < 0.001$). This study provides population-based incidence and comparative survival figures in ET and AMM. Am. J. Hematol. 61:10–15, 1999.

Key words: agnogenic myeloid metaplasia; epidemiology; essential thrombocythemia; outcome; prognosis

INTRODUCTION

Currently, essential thrombocythemia (ET), agnogenic myeloid metaplasia (AMM), and polycythemia vera (PV) are classified as chronic myeloproliferative diseases (CMPDs). Collectively, a clonal process involving a myeloid progenitor cell characterizes these disorders, which are distinguished from chronic myelogenous leukemia (CML) by the absence of t(9;22) and from myelodysplastic syndrome (MDS) by the absence of dyserythropoiesis. Within the context of the CMPDs, an increased red cell mass defines PV, and the presence of substantial medullary fibrosis characterizes AMM. The diagnosis of ET requires the presence of clonal thrombocytosis in the absence of PV, AMM, and CML. Clinically, ET has the most favorable natural history, with the least propensity toward disease progression or leukemic conversion [1,2]. AMM has a worse prognosis than ET, with a more aggressive clinical course characterized by anemia, marked splenomegaly, and cachexia [3]. Thrombohemorrhagic complications are frequent in inadequately treated PV and ET.

Population-based epidemiologic data are limited for CMPDs, especially for ET and AMM. The availability of a unique medical record system in Olmsted County, Minnesota, has supported several disease-oriented epidemiologic studies [4]. Accordingly, we reported previously on

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incidence trends and survival in PV [5]. In the present study, we followed a similar strategy to define the incidence and survival in ET and AMM in a geographically defined, predominantly white U.S. population.

METHODS

Setting

The population of Olmsted County, Minnesota, is served by a largely unified medical care system that has accumulated comprehensive clinical records during an extended period. Olmsted County (1990 population, 106,470) is 144 km southeast of Minneapolis and St. Paul, and approximately 70% of the population resides in the city of Rochester. In 1990, the population was 96% white, with 28% of the population older than 45 years and 11% 65 years or older. The population is mostly middle class, and approximately 82% of the adult population are high school graduates. Except for a higher proportion of the working population being employed in the health care industry, the characteristics of the population of Olmsted County are similar to those of the U.S. white population [6].

Rochester Epidemiology Project

Epidemiologic research is possible in Olmsted County because the city and county are relatively isolated from other urban centers and nearly all medical care is provided to local residents by a few providers. The Mayo Clinic, a major referral center, provides most of this medical care, with more than 1,000 full-time physicians representing every medical and surgical specialty and subspecialty. The Mayo Clinic and its hospitals and the Olmsted Medical Center and its affiliated Olmsted Community Hospital provide comprehensive medical care for the region in every clinical discipline. These institutions have cooperated for the last 30 years to establish a comprehensive and exhaustive medical index of diagnoses and procedures for all residents in Olmsted County. This project is known as the "Rochester Epidemiology Project." The Project has linked the medical records of each patient across providers.

Identification of Cases

The study period was between 1976 and 1995. Cases of either ET or AMM were initially screened for by cross-referencing diagnostic listings in the epidemiologic database. The medical histories of potential cases of ET (204 patients) and AMM (53 patients) were reviewed further to identify those who fulfilled the diagnostic criteria for either ET (39 cases) or AMM (21 cases). The diagnostic criteria for ET included persistent thrombocytosis > 600×10^9/L for at least 6 months, absence of a comorbid condition associated with reactive thrombocytosis, absence of t(9;22) in patients with available cytogenetic studies, and absence of any other chronic myeloid disorder such as PV or MDS. The diagnostic criteria for AMM included presence of bone marrow fibrosis and atypical megakaryocytic hyperplasia, absence of a comorbid condition associated with reactive myelofibrosis, absence of t(9;22) in patients with available cytogenetic studies, and absence of significant dyserythropoiesis.

Analyses

Incidence rates were calculated assuming the entire population of Olmsted County to be at risk. The denominators for the incidence rates were the age- and sex-specific person-years among Olmsted County residents from 1976 to 1995, as obtained by linear interpretation from the decennial census data [7]. Rates were adjusted to the age and sex distribution of the U.S. north central white population in 1990. Survival was calculated according to the Kaplan-Meier product-limit estimator. Expected survival for those of like age and sex was based on decennial survival estimates of U.S. north central whites in 1990 [8]. Observed and expected survival curves were compared by the log-rank test [9].

RESULTS

Essential Thrombocythemia

For the study period, a total of 39 cases of ET were identified (Table I). This group included 25 females and 14 males, with a female-to-male ratio of 1.8:1. This ratio, when adjusted for age, showed no difference in risk. The age- and sex-adjusted incidence rate was 2.53/100,000 population annually (SE = 0.41). The median age at diagnosis was 72 years (range, 17 to 90; 25% = 59 years, 75% = 79 years). The median platelet count at the time of diagnosis was $915{,}000 \times 10^6$/L (range, 649×10^6/L to $1{,}696 \times 10^6$/L). The patients were followed passively through their medical records for a median of 62.9 months after the time of diagnosis (range, 1 to 204; 25% = 20.7 months, 75% = 112.3 months). Of the 39 patients, 24 (61.5%) were alive at the time of latest follow-up. The cause of death was related to complications of the disease in six of the 15 (40%) patients who died: one patient died of leukemic transformation, four of thrombotic complications (two of pulmonary embolism, two of cerebral infarction), and one of gastrointestinal tract hemorrhage. The patient who had transformation to acute leukemia had been treated with 12 mCi of P-32 3 years before transformation. In 19 patients, ET was treated with hydroxyurea taken orally. Treatment was for an average of 59 months (range, 1 to 204 months); none of these patients developed acute leukemia. The 5- and 10-year survival rates were 74.4% and 61.3%, respec-

TABLE I. Cases of Essential Thrombocythemia in Olmsted County, Minnesota, 1976–1995*

Case	Age at Dx, year	Sex	PLT at Dx, $\times 10^9$/L	Length of F/U, months	Anti-PLT therapy	Status at latest F/U	Cause of death
1	84	F	764	22	Hydroxyurea	Dead	Pulmonary embolus
2	76	F	965	126	Hydroxyurea	Alive	
3	80	F	1,216	122	^{32}P	Dead	Adenocarcinoma (unknown primary tumor)
4	88	F	664	19		Dead	CHF
5	73	F		36	^{32}P	Dead	Leukemia
6	59	M	920	153	Hydroxyurea	Alive	
7	69	M	942	8		Alive	
8	79	F	1,696	112	Anagrelide	Alive	
9	79	F	753	43		Dead	Cerebral infarction
10	80	M	962	6	Hydroxyurea	Dead	Cerebral infarction
11	75	F	977	104	Hydroxyurea	Alive	
12	82	F		64	^{32}P Leukeran	Dead	Myocardial infarction, CHF
13	67	F	919	79	Hydroxyurea	Alive	
14	79	F	649	53		Alive	
15	60	M	1,294	173	^{32}P Hydroxyurea Anagrelide	Dead	Prostate cancer
16	68	F	762	116	Hydroxyurea	Alive	
17	73	M	720	15	Hydroxyurea	Alive	
18	59	F	1,158	128	Anagrelide	Alive	
19	72	F	1,017	96	Hydroxyurea	Dead	CHF
20	81	M	1,050	65	Anagrelide	Dead	Infection
21	77	M	1,460	45	Hydroxyurea	Dead	Unknown
22	66	M	850	90	Hydroxyurea	Alive	
23	52	M	865	26	Hydroxyurea	Dead	Upper gastrointestinal tract hemorrhage
24	68	F	773	19	Hydroxyurea	Alive	
25	25	F	994	79		Alive	
26	76	F	713	138	^{32}P Hydroxyurea	Dead	Pulmonary embolus
27	74	F	754	43		Alive	
28	46	F	704	83		Alive	
29	75	M	1,391	20	Hydroxyurea	Dead	Coronary artery disease
30	17	M	1,136	98	Anagrelide	Alive	
31	55	F	910	153		Alive	
32	36	F	1,111	194	Hydroxyurea	Alive	
33	27	F	895	58		Alive	
34	61	F	724	204	Hydroxyurea	Alive	
35	90	M	861	15	^{32}P	Dead	Pneumonia
36	35	M	1,112	38		Alive	
37	27	M	651	1		Alive	
38	70	F		54	Hydroxyurea	Alive	
39	84	F	806	15		Alive	

*CHF, congestive heart failure; Dx, diagnosis; F/U, follow-up; PLT, platelet(s).

tively (95% confidence interval [CI] = 59 to 90 at 5 years and 43.5 to 82 at 10 years). When all causes of death were considered, the decrease in overall survival of patients with ET compared with age-matched controls was significant ($P = 0.012$) (Table II and Fig. 1).

Agnogenic Myeloid Metaplasia

For the study period, 21 cases of AMM were identified (Table III). This group included 13 females and eight males, for a female-to-male ratio of 1.63:1. This ratio, when adjusted for age, showed no significant risk between the two groups. The age- and sex-adjusted incidence rate was 1.46/100,000 population annually (SE = 0.32). The median age at diagnosis was 67 years (range, 43 to 84; 25% = 62 years, 75% = 74 years). The median hemoglobin level at diagnosis was 10.6 g/dL (range, 6.2 to 15.7 g/dL; 25% = 8.2 g/dL, 75% = 11.8 g/dL), and palpable splenomegaly was present in 19 (90.5%) patients. Progressive disease (defined as a decrease in

TABLE II. Characteristics of Chronic Myeloproliferative Disorders*

	AMM[a]	ET[a]	PV[b]
No. of patients, 1976–1995	21	39	50
Median age at Dx (range, year)	67 (43–84)	72 (18–90)	
Males, no.	8	14	31
Females, no.	13	25	19
Median Hb concentration at Dx (range, g/dL)	10.6 (6.2–15.7)	13.8 (8.7–17.1)	
Median platelet count at Dx (range, $\times 10^6$/L)	312 (16–984)	914 (649–1,696)	
Incidence rate (95% CI) (Patients/100,000/year) (U.S. white population 1990)	1.46 (0.82–2.09)	2.53 (1.77–3.40)	2.3 (1.4–2.5)
Median survival, months	36	130	86

*AMM, agnogenic myeloid metaplasia; CI, confidence interval; Dx, diagnosis; ET, essential thrombocythemia; Hb, hemoglobin; PV, polycythemia vera.
[a]Present study.
[b]Data from Ania et al., 1994 [5]. The study period was 1935–1989.

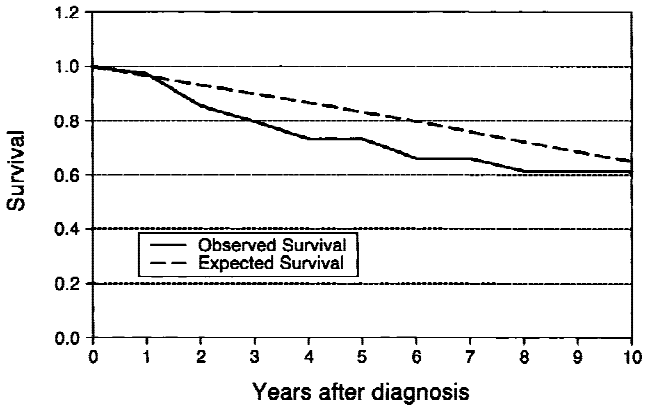

Fig. 1. Survival rate for 39 patients with ET.

hemoglobin of 2 g/dL, progressive splenomegaly, or onset of hypercatabolic symptoms) was observed in 12 patients (57%), with a median time to progression of 7 months (range, 1 to 23 months). The median follow-up period was 33.2 months (range, 0 to 172 months), and at the time of latest follow-up, 14 (67%) patients had died. Of the 14 deaths, five were caused by acute leukemia and three to complications of red cell transfusion. In patients who had transformation to acute leukemia, transformation occurred a median of 33 months (range, 16 to 171 months) after the diagnosis of AMM. Of this group, one had been treated with P-32 and another with melphalan (Alkeran). Treatment with these leukemogenic agents may have increased the rate of transformation in this small population. Survival rate at 3 years was 52.4% (95% CI = 33.9 to 80.9), which was significantly lower than expected for age-matched controls ($P < 0.001$) (Table II and Fig. 2).

DISCUSSION

Many retrospective studies with large patient groups have been published regarding the clinical presentation and natural history of ET [1,10–13] and AMM [13–16]. The epidemiologic information derived from these referral center studies generally underestimates the true population-based incidence. Furthermore, the study samples tended to be biased toward patients who were younger or had other characteristics that made them referable to large academic medical centers. By assigning a stable population base to the denominator and including all diagnosed cases in the community in the numerator of the incidence fraction, we have attempted to avoid potential biases related to case selection and migration and to make our results generalizable to the particular population.

As a result of the aforementioned biases, the incidence rates and median ages at diagnosis in our population are higher than previous estimates [2,3,17]. Other reasons for the higher incidence figures may include our use of less stringent diagnostic criteria and the increasing use of automated counters, which identify asymptomatic cases. In addition, a higher percentage of the population is involved in the health care field, which may lead to a higher degree of "medical scrutiny" than in other populations. Also, it should be noted that the demographic makeup of our study population is more representative of the U.S. white population, and our findings may not pertain to a more diverse ethnic population [6].

The female preponderance in the current study is in agreement with previous studies of ET [10–12,18]. However, when the analysis was adjusted for age, the incidence rates were comparable between the two sexes. The conclusions we can draw about sex predilection are limited because of the limited statistical power of our study. Furthermore, because of treatment implications for women of childbearing age, these patients are usually referred to tertiary medical centers, which is a potential bias of the large studies toward young women. Therefore, the available evidence is not strong for the existence

TABLE III. Cases of Agnogenic Myeloid Metaplasia in Olmsted County, Minnesota, 1976–1995*

Case	Age at Dx, year	Sex	Hb at Dx, g/dL	Splenomegaly, cm below RCM	Length of F/U, months	Status at latest F/U	Cause of death
1	81	F	11.2	5–10	35	Dead	CHF
2	68	M	10.6	<5	48	Alive	
3	84	F	11	<5	52	Dead	CHF
4	63	F	11.5	Not palpable	18	Dead	Gastrointestinal tract hemorrhage
5	74	F	15.7	<5	172	Dead	Anemia
6	65	F	12.7	Not palpable	46	Dead	Lung cancer
7	62	F	11.8	<5	113	Alive	
8	83	F	7.3	<5	6	Dead	Not known
9	71	M	8.2	5–10	37	Dead	Prostate cancer
10	73	M	10.8	<5	15	Alive	
11	74	F		>10	8	Dead	AMM
12	70	F	10.4	5–10	16	Dead	Pneumonia
13	77	F	8.9	5–10	19	Dead	AML
14	63	M	7	5–10	33	Dead	AML
15	52	F	8.3	>10	2	Dead	Myocardial infarction
16	62	F	15	<5	54	Dead	AML
17	72	M	6.2	<5	11	Dead	AMM
18	66	M	11.8	>10	65	Alive	
19	60	M		5–10	43	Alive	
20	43	M	10.2	>10	0	Alive	
21	60	F	7.8	>10	22	Alive	

*AML, acute myelogenous leukemia; AMM, agnogenic myeloid metaplasia; CHF, congestive heart failure; Dx, diagnosis; F/U, follow-up; Hb, hemoglobin; RCM, right costal margin.

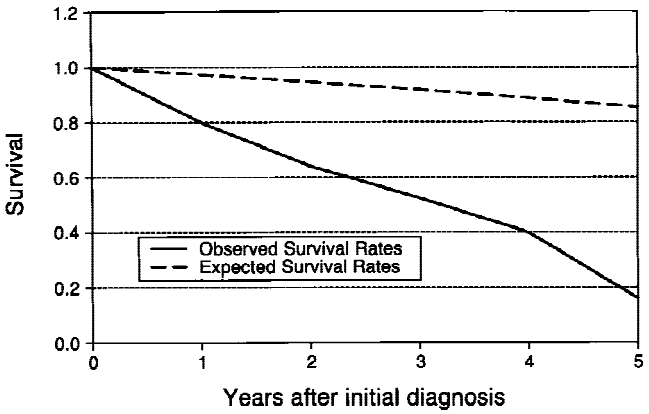

Fig. 2. Survival rate for 21 patients with AMM.

in ET of a biologic basis of a predilection for females.

The increase in mortality for both ET and AMM compared with age-matched controls was statistically significant. Our observation differs from that of a previous report, which suggested a normal life expectancy for patients with ET [13]. In that report, there was a large group of patients (247) but a shorter follow-up period (median, 27 months). In addition, the death rate was higher in the group with ET than in normal controls (37 vs. 30 deaths), but this was not statistically significant. Therefore, a longer follow-up in the Rozman et al. study [13] may have shown decreased survival of patients with ET in comparison with the normal population, as evident in our study. This is similar to what is observed in PV, in which decreased survival becomes more evident in the later stages of the disease [5,13,19].

The current study complements our previous report on incidence trends in PV [5]. Together, these two studies provide population-based incidence and mortality rates. From these studies, it is apparent that comparative treatment trials in ET or PV may require long periods of time not only to accrue the necessary number of patients but also to appreciate potential differences in survival.

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